Oral Estrogen Class Review

Indications:

The following table lists the FDA approved indications for the class:

Indication: / Product:	Moderate-to-severe vasomotor symptoms associated with menopause	Moderate-to-severe vasomotor symptoms associated with menopause in patients not improved with estrogens alone	Vulval and vaginal atrophy	Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure	Breast cancer with metastatic disease (palliation only)	Advanced androgen-dependent prostate cancer (palliation only)	Osteoporosis prevention
Esterified Estrogens (Estratab®, various)	X		X	X	X	X	X
Micronized Estradiol (Estrace®, various)	X		X	X	X	X	X
Estropipate (Ogen®, various)	X		X	X			X
Ethinyl Estradiol (Estinyl®)	X			X*	X†	X†	
Synthetic Conjugated Estrogens A (Cenestin™)	X						
Conjugated Estrogens [Equine] (Premarin®)	X		X	X	X	X	X
Estradiol plus Norgestimate (Ortho-Prefest™)	X		X				X
Estradiol plus Norethindrone Acetate (Activella™)	X		X				X
Ethinyl Estradiol plus Norethindrone Acetate (Femhrt™)	X						X
Conjugated Estrogens plus Medroxyprogesterone Acetate (PremPro®)	X		X				X
Conjugated Estrogens plus Medroxyprogesterone Acetate (PremPhase®)	X		X				X
Esterified Estrogens plus Methyltestosterone (Estratest®)		X					
Esterified Estrogens plus Methyltestosterone (Estratest HS®)		X					

* Indicated for female hypogonadism only.

† These indications do not specifically list metastatic disease for breast cancer or androgen-dependent prostate cancer. However, Estinyl® is indicated for palliative therapy in inoperable, progressive disease.

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Unlabeled Uses: (include but are not limited to)

- Hypercholesterolemia in postmenopausal women.
- Uterine bleeding (abnormal) associated with a hypoplastic or atrophic endometrium without organic pathology.
- Estratest®, Estratest HS®- Osteoporosis prevention and postpartum breast engorgement. In November 1998 the FDA withdrew approval of estrogen-containing products for the prevention of postpartum breast engorgement under the recommendation of the Fertility and Maternal Health Drugs Advisory Committee (Federal Register, 1998).

Pharmacology / Estrogen Source:

Single-Entity Products

Single-entity products contain various estrogens. Estrogens are essential to the development and maintenance of the female reproductive system and secondary sex characteristics. Estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The ovarian follicle is the primary source of estrogen in the normally cycling adult woman, responsible for secreting 70-500 µg of estradiol daily. Declining estrogen secretion during menopause is associated with signs and symptoms of hormone deficits in estrogen-dependent organs (female genital organs, breasts, hypothalamus, pituitary). Pituitary gonadotropin secretion rises, reflected by increased quantities of gonadotropin in blood and urine. The endometrium becomes atrophic, myometrial mass decreases, and the vaginal epithelium becomes thin. Postmenopausal estrogen use relieves symptoms of estrogen depletion (e.g. vasomotor symptoms, atrophic vaginitis) and reduces the risk of severe coronary heart disease (Lauritzen, 1976; Grodstein, 1999). Estrogens also reduce the rate of bone loss in postmenopausal women and reduce bone fractures (Christiansen, 1980; Kiel, 1987). Estrogen deficiency in women without a uterus is most often treated with unopposed estrogen therapy. Marketed products are as follows:

Estratab® (esterified estrogens) is composed of a mixture of sodium salts of the sulfate esters of the estrogenic substances, primarily estrone sulfate (75-85%) and equilin sulfate (6-15%) that are prepared synthetically from plant (soybean and Mexican yam) sterol precursors.

Estrace® (micronized estradiol) is composed of micronized synthetic 17 beta-estradiol.

Ogen® (estropipate) is prepared from purified crystalline estrone, solubilized as a sulfate and stabilized with piperazine. Estropipate was formerly known as piperazine estrone sulfate.

Estinyl's® (ethinyl estradiol) estrogen component is a semisynthetic estrogen derived from the addition of an ethinyl group on the estradiol molecule.

Cenestin™ (synthetic conjugated estrogens A) is a blend of nine estrogens derived from plant sources (soybean and yam).

Premarin® (conjugated estrogens) is composed of conjugated equine estrogens obtained from the urine of pregnant mares and purified. Premarin® contains 28 known steroidal components, the major components being sodium estrone sulfate (50-63%) and sodium equilin sulfate (22.5-32.5%). The product also contains progestins and androgens.

Combination Products

Most combination products contain estrogens with progestins. Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local estrogen metabolism to less active metabolites, or inducing gene products that blunt the response to estrogens. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, bone, skeletal tissue, and central nervous system. Progestins produce similar endometrial changes to those of the naturally occurring hormone progesterone. In women with an intact uterus, the use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial cancer (Buring, 1986). The addition of progestin to an estrogen replacement regimen reduces the incidence of endometrial hyperplasia, and the attendant risk of cancer in women with intact uteri (Woodruff, 1994). Adding a progestin to an estrogen replacement regimen has not been shown to interfere with the efficacy of estrogen replacement therapy for its approved indications.

Some progestins are available as individual marketed products. Recently, for convenience, combination products have been marketed. Marketed products are as follows:

Activella™ (estradiol plus norethindrone acetate) and Ortho-Prefest™ (estradiol plus norgestimate) utilize synthesized estradiol as their estrogen component.

Femhrt's™ (ethinyl estradiol plus norethindrone acetate) estrogen component is synthesized from sitosterol, a compound extracted from soybeans.

PremPro® and PremPhase® (conjugated estrogens plus medroxyprogesterone acetate) utilize the same conjugated estrogens that are found in Premarin®.

Some combination products contain androgens. Androgens have both reproductive and non-reproductive effects and are present in substantial amounts in women. The ovary and the adrenal cortex synthesize small amounts of testosterone. Methyltestosterone, a synthetic derivative of testosterone, has predominant anabolic and minor androgenic activity. Preliminary data suggest a beneficial role for androgens in regard to CNS function. They have positive effects on mood, cognition, memory, and libido. The mechanisms by which androgens affect the CNS are unclear. Testosterone binds to the androgen receptor, it can be aromatized to estradiol, and it can be converted to the more potent androgen, dihydrotestosterone. It appears that all three of these mechanisms are involved in the CNS effects of androgens. The distribution of androgen receptors, estrogen receptors, and progesterone receptors in the CNS is thought to result in an intricate control pattern (Plouffe, 1998; Sherwin, 1998). Androgen receptors are also found in osteoblasts and the combination of androgens and estrogens can increase bone mass. Postmenopausal women treated with estrogen plus testosterone have a greater increase in bone

mineral density in the hip and lumbar spine than those treated with estrogen alone (Barrett-Connor, 1999). Available products are as follows:

Estratest® and Estratest HS® (esterified estrogens plus methyltestosterone) utilize the same esterified estrogens found in Estratab®.

Reviewer's Note: The FDA has announced that it will not approve generic forms of conjugated estrogens because generic versions cannot be shown to contain the same active ingredients as Premarin® (USHHS, 1997). Premarin® contains a number of different estrogens. How each of these components contributes to Premarin's® overall effectiveness has not been adequately explored. Many experts believe that sodium estrone sulfate and sodium equilin sulfate are the primary active ingredients in Premarin®; these are the only two ingredients listed by the United States Pharmacopeia (USP) as active. Delta 8,9 dehydroestrone sulfate (DHES) is listed in the USP as an impurity. However, Wyeth-Ayerst claims that the absence of delta 8,9 DHES makes products compositionally different from the innovator drug. The FDA has requested that Wyeth-Ayerst further characterize the components of Premarin®; Wyeth-Ayerst has committed to do so, although there is no timeframe for completion.

Cenestin™ was originally formulated to be a generic version of Premarin®. Because of the 1997 FDA position on approval of an abbreviated new drug application (ANDA) for conjugated estrogens, Duramed filed a NDA for Cenestin™. On March 24th 1999 the FDA approved Cenestin™ for use at doses ranging from 0.625-1.25 mg. The FDA assigned the designation "conjugated estrogens, A." (Subsequent approvals of synthetic conjugated estrogens will be distinguished by B, C, D, etc.) No new conjugated estrogen product will be labeled USP until a drug monograph for the entire class is adopted. Therefore, Cenestin™ is not a generic form of Premarin®, will be listed separately from Premarin® in the Orange Book, and will not be listed with a TE code (Anonymous, 1999).

Pharmacokinetics:

Exogenous estrogens and their esters are handled within the body in essentially the same manner as the endogenous hormones. Metabolic conversion of estrogens occurs primarily at the liver, but also occurs at local target tissue sites. Complex metabolic processes result in an equilibrium between conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and unesterified forms. When given orally, naturally occurring estrogens and their esters circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens are degraded very slowly in the liver and other tissues, resulting in a higher intrinsic potency. The pharmacokinetic parameters of the various estrogen products are presented in the following table. The clinical significance of these differences is unclear.

Pharmacokinetic parameters of estrogen components:

Drug	Dose	Component*	C_{max}	T_{max} (h)	$T_{1/2}$ (h)	AUC
Estratab®	0.625 mg	Estrone	8.6 ng/mL	6.8	12.1	107 ng·hr/mL
		Equilin	2.0 ng/mL	4.7	10.0	16 ng·hr/mL
Estrace®	1.0 mg	Estrone	200 pg/mL	6.0	---	---
		Estradiol	40-50 pg/mL	5.0	---	---
Cenestin™	2x 0.625 mg	Estrone†	4.4 ng/mL	7.7	10.6	70 ng·hr/mL
		Equilin	3.3 ng/mL	5.8	9.7	47 ng·hr/mL
Premarin®	2x 0.625 mg	Estrone	7.3 ng/mL	7.3	15.0	134 ng·hr/mL
		Equilin	5.0 ng/mL	6.2	10.1	65 ng·hr/mL
Ortho-Prefest™	1/.09	Estrone	285 pg/mL	6	---	4153 pg/mL·hr
		Estradiol	39.3 pg/mL	7	---	681 pg/mL·hr
Activella™	1/0.5 mg	Estradiol†	34.6 pg/mL	6.8	13.2	1053 pg/mL·hr
		Estrone	251.1 pg/mL	5.7	12.2	5223 pg/mL·hr
Femhrt™	1/.1‡	Ethinyl est.	38.3 pg/mL	1.8	23.9	471 pg·hr/mL
PremPro®	2x 0.625/2.5	Estrone	6.6 ng/mL	6.1	20.7	116 ng·hr/mL
		Equilin	5.1 ng/mL	4.6	11.4	50 ng·hr/mL
PremPhase®	2x 0.625/5.0	Estrone	6.3 ng/mL	9.1	23.6	151 ng·hr/mL
		Equilin	4.2 ng/mL	7.0	17.2	72 pg·hr/mL
Estratest®	1.25/2.5	Estrone	21.3 ng/mL	6.1	14.1	---
		Equilin	4.1 ng/mL	5.2	13.0	---

* Estrone and equilin values represent conjugated estrogens, uncorrected for baseline

† Estrone value for Cenestin™ represents conjugated estrogens, corrected for baseline; estradiol values for Activella are adjusted for baseline.

‡ Not an FDA-approved dosage

Cenestin™ was originally formulated to mimic the release properties of Premarin®. The Premarin® formulation is not dose proportional; the concentration/time profile obtained from two 0.625 mg tablets is not equivalent to that obtained from one 1.25 mg tablet. After the FDA decided not to approve generic versions of conjugated estrogens, it asked Duramed to reformulate the 1.25 mg dose of Cenestin™ so that its tablet strengths would be dose proportional.

Efficacy:
Comparative efficacy will be reviewed by indication. The following studies provide a representation of published (in full) clinical trials and are by no means all-inclusive. Data on the other products are available in abstract, the manufacturer's printed product material, the package inserts and as data on file from the manufacturer. (These data were not included in these tables).

For the treatment of moderate-to-severe vasomotor symptoms associated with menopause:

Study / Design / Subjects	Intervention	Results	Conclusion / Comments
Watts et al, 1995 Multicenter, randomized, double-blind, clinical trial to assess the efficacy of Estratab® and Estratest® on bone, lipids, and menopausal symptoms. Duration = 2 years 66 women who had bilateral oophorectomy and hysterectomy Ages 21-60, avg. late 40's Menopausal symptoms assessed using a 0-7 point scale.	Estratab® 1.25 mg/d (N=33) Estratest® 1.25/2.5 qd (N=33)	Intensity scores for individual somatic symptoms such as hot flashes, insomnia, and vaginal dryness decreased significantly from baseline in both groups within one month and persisted throughout the study period. There was no significant difference between the two treatment groups. Estratest® subjects were significantly more likely to experience acne or facial hair growth than the Estratab® group.	Both Estratab® and Estratest® were both shown to effectively reduce menopausal symptoms when compared to baseline.
Raisz et al, 1996 Multicenter, randomized, open-label trial to assess the effectiveness of Estratest® and Premarin® on bone formation/resorption, lipids, and menopausal effects. Duration = 9 weeks 28 postmenopausal women Ages 46-80 > 5 years since last menstrual period No estrogens last 6 months Modified Menopausal Index to assess menopausal symptoms	Estratest® 1.25/2.5 qd (N=13) Premarin® 1.25 mg/d (N=15)	Patients in the Estratest® group reported more severe symptoms of menopause at baseline and were significantly different than those in the Premarin® group. Estratest® produced significant reductions in the somatic, psychosomatic, and psychological symptoms of menopause from baseline. Premarin® produced a significant reduction in the somatic symptoms of menopause from baseline only.	Patients receiving Premarin® and Estratest® experienced improvements in the somatic symptoms of menopause. Patients receiving Estratest® also showed improvements in the psychosomatic and psychological symptoms of menopause. Significant differences in the two treatment groups at baseline limits the direct comparison.

Study / Design / Subjects	Intervention	Results	Conclusion / Comments
Coupe et al, 1975 Randomized, double-blind, crossover trial to assess the effects of Premarin® on menopausal symptoms and blood clotting. Duration = 6 months 30 peri- and postmenopausal women Average age 52 Menopausal Index to assess menopausal symptoms	Group 1: Premarin® 1.25 mg/d for 21 days, followed by 7 days off for 3 months. (N=15) Group 2: Placebo for 3 months. (N=15) After three months subjects switched over to the other treatment group for three months.	The symptom index score was reduced significantly from baseline after three groups in both Group 1 and Group 2. There were no significant differences between the two groups after three months. In the second three months of the trial, Group 2 subjects showed continued improvement in index score, while the index score of Group 1 subjects declined. The two groups were not significantly different overall, although Group 2 subjects had significantly greater improvements in arthralgias, palpitations, depression, and parastesias than Group 1 patients in the second three months. Side effects were similar between the active and placebo treatment groups.	Premarin® users experienced significant improvements in menopausal symptoms when compared to baseline. However, overall symptom score was not significantly different than placebo during the study; some individual menopausal symptoms improved significantly better than placebo in the second half of the study. Large placebo effect makes any benefit of Premarin® difficult to detect with a small sample.
Lozman et al, 1971 Multicenter, randomized, double-blind, crossover trial to assess the efficacy of Ogen® and Premarin® on vaginal cytology and the relief of menopausal symptoms. Duration = 2 months 168 estrogen-deficient women with menopausal symptoms Average age 49 Subject interview used to assess response to therapy.	Group 1: Ogen® 3 mg/d for 21 days, followed by 7 days off. (N=84) Group 2: Premarin® 1.25 mg/d for 21 days, followed by 7 days off. (N=84) After one month, subjects switched over to the other treatment group for one month.	Both agents were effective in reducing target symptoms in study subjects. Patients reported less severe flushing and sweating while on Premarin® therapy, less severe insomnia while on Ogen® therapy, and similar results on headaches, depression, and anxiety on both agents. 58 subjects preferred Ogen® therapy, 26 preferred Premarin® therapy, and 33 had no preference. Three Premarin® subjects discontinued therapy due to side effects, two discontinued due to uncontrolled symptoms. One Ogen® subject discontinued therapy due to side effects, none discontinued due to uncontrolled symptoms.	Premarin®and Ogen® were both effective for reducing menopausal symptoms. Patients preferred Ogen® to Premarin® by a 2-1 margin. Statistical significance of many of the results were not examined, limiting the ability to directly compare the two agents.

Study / Design / Subjects	Intervention	Results	Conclusion / Comments
Martin et al, 1972 Multicenter trial to assess the effectiveness, tolerance, and patient preference of Estrace®, Premarin®, two progestin products, and placebo. Duration = 5 months 71 women Subject interview used to assess response to therapy.	All subjects received Estrace® 2 mg/d for 21 days, followed by 7 days off. Subjects then received the following regimens for 21 days, followed by 7 days off over the following 4 months: Premarin® 1.25 mg/d Norquens® 100/2 qd Norinyl® 2 mg/d Placebo	85% of subjects reported their well-being as excellent or good, 76% reported no hot flashes, and 98% reported acceptable bleeding patterns while on Estrace® therapy. 40% of subjects preferred Estrace® therapy, 20% preferred Premarin®, 15% preferred Norquens®, and 9% preferred Norinyl®.	More subjects preferred Estrace® therapy to the other therapies in the study. Subject characteristics are not listed. Effectiveness of other agents was not described. Statistical significance not calculated. Study design biased towards Estrace® as all patients received it first.
Barrett-Connor et al, 1999 Multicenter, randomized, double-blind trial to assess the effectiveness of Premarin®, Estratest®, and Estratest HS® on BMD, menopausal symptoms, and lipid profiles. Duration = 2 years 311 women who had bilateral oophorectomy and hysterectomy Average age 45 Modified menopausal index used to assess menopausal symptoms.	Premarin® 0.625 mg/d (N=79) Premarin® 1.25 mg/d (N=78) Estratest HS® 0.625/1.25 qd (N=81) Estratest® 1.25/2.5 qd (N=73) All patients received supplemental calcium, 1000 mg/d	Subjects in all four treatment groups reported an improvement in menopausal symptoms and quality of life measures at 24 months. Improvement in somatic symptoms (hot flashes, sweats, vaginal dryness), psychosomatic symptoms (sleeplessness, headache, feelings of suffocation) and psychological symptoms did not differ between the groups. Side effects were infrequent; the only significant difference between treatment groups was a higher incidence of nausea in the Premarin® groups (11% and 22%) compared to the Estratest HS® (6%) and Estratest® (3%) groups. 45 subjects discontinued medication due to adverse events; there was no significant difference between treatment groups.	Premarin®, Estratest®, and Estratest HS® were similarly efficacious for the treatment of menopausal symptoms in menopausal women. A comparative table of patient scores across the four treatment groups was not included.

Study / Design / Subjects	Intervention	Results	Conclusion / Comments
Sulak et al, 1999 Multicenter, randomized, double-blind trial to assess the efficacy of Ortho-Prefest™ and estradiol on bleeding and vasomotor symptoms. Duration = 3 months 1,253 postmenopausal women Average age 54 > 12 mos. since last menstrual period No HRT last 8 weeks Vasomotor symptoms evaluated by patient diary.	Estradiol 1 mg/d (N=311) Ortho-Prefest™ 1/.09* (N=313) * Continuous repetition of the administration of estradiol 1 mg/d for 3 days followed by estradiol 1 mg/d plus norgestimate 0.09 mg/d for 3 days for three months. Two other doses of Ortho-Prefest™ were examined in this dose-ranging study (1/0.03 and 1/0.18)	Among those subjects who experienced vasomotor symptoms at baseline, there was no significant difference between estradiol (70%) and Ortho-Prefest™ (76%) in the percentage of patients who were asymptomatic at three months. Adverse events were similar between the two groups. Subjects receiving Ortho-Prefest™ were more likely to report breast pain (19%) than those receiving estradiol (13%).	Ortho-Prefest™ is as effective as estradiol monotherapy for the treatment of vasomotor symptoms associated with menopause.
Archer et al, 1992 Multicenter, randomized, double-blind trial to assess the efficacy of Estrace® and Premarin® for the treatment of vasomotor symptoms associated with menopause. Duration = 13 weeks 128 naturally or surgically menopausal women Mean age 50 Patient diary used to track frequency of menopausal symptoms	Following a one-week pretreatment screening phase, patients were randomized to one of the following regimens: Estrace® 1.0 mg/d (N=27) Estrace® 2.0 mg/d (N=25) Premarin® 0.625 mg/d (N=27) Premarin® 1.25 mg/d (N=26) Placebo (N=25)	The daily frequency of vasomotor effects decreased in all treatment groups during the 12-week trial. At week 12 there was no significant difference in the decrease of vasomotor events between Estrace® 1.0 mg/d (91% reduction), Estrace® 2.0 mg/d (92%), Premarin® 0.625 mg/d (80%), and Premarin® 1.25% (95%). All active treatment groups were significantly more effective than placebo (66%). More physicians and patients reported having an excellent or good response to Estrace® 2mg/d (100%) as compared to Premarin® 1.25 mg/d (84%). No differences were seen in adverse events between Estrace® and Premarin®.	Estrace® and Premarin® are similarly efficacious and more effective than placebo for the treatment of vasomotor symptoms associated with menopause.

The reviewer was unable to locate any trials published in full examining the efficacy of Cenestin™, Femhrt™, Activella™, Estinyl®, PremPro®, or PremPhase® for this indication. However the various manufacturers product information documents and abstracts are available.

A published abstract (Stevens, 1998) evaluates the efficacy of Cenestin™ in the treatment of vasomotor symptoms. In a randomized, double-blind, multicenter, placebo-controlled trial, 120 perimenopausal or postmenopausal women received either 0.625 mg Cenestin™ or placebo for 12 weeks. Dose titration based on response was permitted after 1 week of treatment. Cenestin™ was significantly better than placebo for the treatment of moderate-to-severe vasomotor symptoms. Most women required a dose of 1.25 mg daily.

The clinical product monograph for Femhrt™ (Warner-Lambert, 2000) reviews its efficacy on vasomotor symptoms. In a 12-week, randomized, double-blind, placebo-controlled trial, 266 women received Femhrt™ or placebo. Femhrt™ significantly reduced the incidence of hot flash frequency, hot flash intensity, and night sweats when compared to placebo.

The prescribing information for Activella™ (Pharmacia, 2000) reviews its efficacy on vasomotor symptoms. In a 12-week, randomized, placebo-controlled trial, 92 women received Activella™, 1 mg/d of estradiol, or placebo. The Activella™ group and the estradiol group experienced a significant reduction in the mean number and intensity of hot flushes from baseline compared to placebo.

A one-year, multicenter, double-blind randomized trial (Archer, 1994) compared the bleeding control obtained with PremPro® 0.625/2.5 and 0.625/5.0, PremPhase® 0.625/5.0, or Premarin® 0.625 mg/d in 1,724 postmenopausal women. Subjects who received PremPro® experienced amenorrheic cycles 61.4% and 72.8% of the cycles, respectively; those receiving Premarin® were amenorrheic 75.5% of the cycles. Subjects receiving PremPhase® experienced amenorrhea 16.1% of the cycles, and experienced irregular bleeding [bleeding occurring at any time other than the period of expected withdrawal bleeding] during 8.1% of the cycles.

For the treatment of moderate-to-severe vasomotor symptoms associated with menopause not improved with estrogens alone:

Study / Design / Subjects	Intervention	Results	Conclusion / Comments
Sarrel et al, 1998 Randomized, double-blind clinical trial to assess the effectiveness of Estratest® on women dissatisfied with their estrogen or estrogen-progestin therapy. Duration = 8 weeks 20 postmenopausal women Average age 52 Chief complaint of lowered sexual drive or satisfaction. Sexual Activity and Libido Scale used to assess frequency / satisfaction	Active treatment was preceded by a two week observation therapy on previously prescribed estrogen therapy and a two week placebo washout period. Estratab® 1.25 mg/d (N=11) Estratest® 1.25/2.5 mg/d (N=9)	Patients receiving Estratest® experienced statistically significant improvement in the combined ratings of sexual sensation and desire and sensation alone at the end of the study compared to previous estrogen therapy and from placebo baseline. Improvement in desire alone was significantly improved at study end compared to previous estrogen therapy, but not placebo baseline. No statistically significant differences were seen in menopausal symptoms, incidence of vaginal bleeding, relief of hot flashes, or disturbed sleep.	Estratest® increased sexual sensation and desire in postmenopausal women who experienced lowered sexual drive and satisfaction while on estrogen replacement therapy.

For the treatment of hypoestrogenism due to hypogonadism, castration, or primary ovary failure:
No studies published in full could be located investigating the efficacy of this class for the treatment of hypoestrogenism due to hypogonadism, castration, or primary ovary failure.

For the treatment breast cancer with metastatic disease (palliation only):
No studies published in full could be located investigating the efficacy of this class for the treatment breast cancer with metastatic disease (palliation only). The studies that were conducted on the estrogens for this indication occurred in the 1940's and 1950's, often focused on diethylstilbestrol, and primarily consisted of case reports.

For the treatment of advanced androgen-dependent prostate cancer (palliation only):
Arm three of the Veterans Administration Cooperative Urological Research Group studies (Byar, 1988) examined hormonal therapy in 1,112 patients with stage III or IV prostate cancer. These patients were randomized to one of four treatment groups: Premarin® 2.5 mg/d, Provera® 30 mg/d, diethylstilbestrol (DES) 1.0 mg/d, or DES 1.0 mg/d plus Provera® 30 mg/d. Although there were no significant differences in overall survival between treatments, 1.0 mg/d DES was somewhat more effective than 2.5 mg/d of Premarin® or 30 mg/d Provera® in retarding progression from stage III to stage IV.

For the prevention of osteoporosis:

Study / Design / Subjects	Intervention	Results	Conclusion / Comments
The PEPI Writing Group, 1996 Multicenter, randomized, double-blinded, placebo controlled clinical trial to assess the effects of hormone replacement therapy on BMD. Duration = 36 months 875 postmenopausal women Ages 45-64 1-10 years since last menstrual period No estrogens or progestins last 2 mos. BMD assessed at spine and hip.	Premarin® 0.625 mg/d (N=175) Premarin® 0.625 mg/d + MPA 10 mg/d for 12d/mo (N=174) Premarin® 0.625 mg/d + MPA 2.5 mg/d (N=174)* Premarin® 0.625 mg/d + MP 200 mg/d for 12d/mo (N=178) Placebo (N=174) *same regimen as Prempro® 0.625/2.5	Compliance to therapy varied among the groups; at the 36 month visit 78% of women on combo therapy, 74% on placebo, and 56% on estrogen only were taking assigned medication. Among adherent subjects at 36 months: Spine BMD: Placebo: –2.8% Active treatment: +5.1% Hip BMD: Placebo: –2.2% Active treatment: +2.3% No active treatment group was significantly different from any other active treatment group.	Hormone replacement therapy using Premarin® and Premarin®-progestin combinations increased BMD at clinically important sites when compared to placebo. Reasons for poorer adherence of patients on Premarin® monotherapy not explored.
Genant et al, 1997 Multicenter, randomized, double-blind, placebo controlled clinical trial to assess the effects of Estratab® on BMD, lipid levels, and endometrial structure. Duration = 24 months 406 postmenopausal women Average age 51 ½-4 years since last menstrual period No estrogens last 2 months No smokers BMD assessed: lumbar spine and hip	Estratab® 0.3 mg/d (N=101) Estratab® 0.625 mg/d (N=102) Estratab® 1.25 mg/d (N=100) Placebo (N=103) All patients received supplemental calcium, 1000 mg/d	No differences were seen in compliance among the four groups; at least 94% of subjects in each group were compliant. Among all subjects at 24 months: Spine BMD: Placebo: – 2.5% ETB 0.3 mg/d: +1.76% ETB 0.625 mg/d: +2.81% ETB 1.25 mg/d: +5.10% Hip (total) BMD: Placebo: –0.77% ETB 0.3 mg/d: +1.48% ETB 0.625 mg/d: +2.43% ETB 1.25 mg/d: +3.38% All Estratab® groups are significantly greater than placebo, and 1.25 mg/d Estratab® is significantly greater than lower-dose Estratab® for spine BMD.	Estrogen replacement therapy using Estratab® resulted in increased BMD in the spine and hip when compared to placebo.

Study / Design / Subjects	Intervention	Results	Conclusion / Comments
Quigley et al, 1987 Multicenter, open-label trial to assess the efficacy of Estrace® and Premarin® on BMD. Duration = 3 years 397 postmenopausal women Ages 51-80 BMD measured at distal radius	Patients were educated about the pros and cons of estrogen use in the prevention of osteoporosis and were then allowed to choose on of the following regimens: Estrace® 1 mg/d (N=169) Premarin® 0.625 mg/d (N=124) Placebo (N=104) All patients received supplemental calcium, 1,000 mg/d (receiving estrogen) or 1,500 mg/d (receiving placebo).	Both Estrace® and Premarin® provided equal protection against bone loss. The subjects receiving placebo lost bone three times as rapidly as Estrace® or Premarin® users. Among evaluable subjects at 36 months: 51-60 year olds Radial BMD: Placebo: -2.0%/yr ECE, PRM: -0.5%/yr 61-70 year olds Radial BMD: Placebo: -2.6%/yr ECE, PRM: -0.7%/yr 71-80 year olds Radial BMD: Placebo: -1.0%/yr ECE, PRM: -0.9%/yr Result data for Estrace® and Premarin® are not presented separately; they are only shown as a combined group.	Estrace® and Premarin® are equally efficacious and more effective than placebo in the prevention of BMD loss at the radius. Those patients who received estrogen therapy between the ages of 51-60 experienced a lesser decline in radial BMD than older patients. Absence of separated data for the two estrogens limits the ability to directly compare the two agents.
Speroff et al, 1996 Multicenter, randomized, double-blind, placebo controlled clinical trial to assess the effects of Femhrt™ on BMD, lipids, and endometrial effects. Duration = 24 months 1,265 postmenopausal women Average age 51 No estrogens last 6 months BMD assessed at lumbar spine	Patients were randomized to one of eight treatment groups (four groups of varying dose unopposed estrogen, four groups of varying dose estrogen-progestin) or placebo. Each group had 136 to 147 subjects. All patients received supplemental calcium, 1000 mg/d	695 women had evaluable BMD data. The 0.01 mg/d ethinyl estradiol group was terminated early due to a high rate of endometrial hyperplasia. Among evaluable subjects at 24 months: Lumbar BMD: Placebo: -7.4% FEM 1/0.05: +2.2% FEM 1/0.1: +4.2% The Femhrt™ 1/0.05 and 1/0.1 groups increased BMD significantly from baseline, and the Femhrt™ 0.5/0.025, 1/0.05, and 1/0.1 groups were significantly better than placebo.	Hormone replacement therapy using Femhrt™ produced a significant increase in lumbar BMD that was not present with unopposed estrogen treatment.

Study / Design / Subjects	Intervention	Results	Conclusion / Comments
Raisz et al, 1996 Multicenter, randomized, open-label trial to assess the effectiveness of Estratest® and Premarin® on bone formation/resorption, lipids, and menopausal effects. Duration = 9 weeks 28 postmenopausal women Ages 46-80 > 5 years since last menstrual period No estrogens last 6 months BMD assessed at lumbar spine	Estratest® 1.25/2.5 qd (N=13) Premarin® 1.25 mg/d (N=15) Supplemental calcium was added to bring the average daily intake to 1000-1500 mg/d	Effects on bone resorption were not significantly different between the two groups. Premarin® patients showed decreases in serum markers of bone formation (alkaline phosphatase, osteocalcin, and C-terminal procollagen peptide). Estratest® patients showed increases in these markers.	Markers for bone formation were improved over baseline for those patients receiving Estratest®, while patients receiving Premarin® saw these markers decrease. Small sample size and short duration of trial limits applicability of results.
Delmas et al, 2000 Multicenter, randomized, double-blind, placebo controlled trial to assess the efficacy of Activella™ on postmenopausal bone loss and turnover. Duration = 2 years 135 postmenopausal women Mean age 58 > 1 year since last menstrual period BMD measured at lumbar spine, hip, distal radius, and total body.	Activella™ 1/0.5 qd (N=46) Activella™ 1/0.25 qd* (N=44) Placebo (N=45) All subjects received supplemental calcium, 500 mg/d * not an FDA-approved dose	Among all subjects at 2 years: Lumbar BMD: Placebo: -0.9% Activella™ 1/0.5: +5.4 % Activella™ 1/0.25: + 5.2 % Total Hip BMD: Placebo: -1.2 % Activella™ 1/0.5: +3.3 % Activella™ 1/0.25: +3.1 % Both strengths of Activella™ were significantly more effective than placebo for those parameters, as well as distal radius and total body BMD.	Activella™ is significantly more effective than placebo in preventing bone loss in postmenopausal women.

The reviewer was unable to locate any fully published trials examining the efficacy of Ogen®, Ortho-Prefest™, or PremPhase® for this indication.

Lipid Effects:

The following effects on lipid profiles have been seen among the estrogens:

	Dose	N	Total Chol.	HDL-C	LDL-C	Triglycerides
Estratab® (Genant, 1997)	0.3	101	-5.7 mg/dL	+2.7 mg/dL	-8.9 mg/dL	+4.5 mg/dL
Estratab® (Genant, 1997)	0.625	102	-1.3 mg/dL	+5.5 mg/dL	-6.9 mg/dL	+3.8 mg/dL
Estratab® (Genant, 1997)	1.25	100	-13.4 mg/dL	+5.9 mg/dL	-24.5 mg/dL	+26.0 mg/dL
Estratab® (Watts, 1995)	1.25	23	-5.2 mg/dL	+6.7 mg/dL	-11.9 mg/dL	+19.5 mg/dL
Estrace® (Walsh, 1991)	2.0	9	-4.0 mg/dL	not listed	-16.7 mg/dL	+16.3 mg/dL
Ogen® (Bagdade, 1991)*	1.25	6	-6.9 %	-3.8 %	not examined	+5.9 %
Estinyl® (Speroff, 1996)*	0.05	128	+2.3 %	+18.5 %	-6.8 %	+38.7 %
Premarin® (PEPI Group, 1995)	0.625	175	-7.6 mg/dL	+5.6 mg/dL	-14.5 mg/dL	+13.7 mg/dL
Premarin® (Barrett-Connor, 1999)	0.625	61	-6.1 mg/dL	+7.2 mg/dL	-20.3 mg/dL	+36.7 mg/dL
Premarin® (Raisz, 1996)	1.25	13	-6.5 %	+22.1 %	-24.1 %	+34.2 %
Premarin® (Barrett-Connor, 1999)	1.25	61	+6.3 mg/dL	+9.7 mg/dL	-13.1 mg/dL	+40.4 mg/dL
Ortho-Prefest™ (Lobo, 2000)	1/.09	31	-1.9 %	+9.7 %	-4.9 %	+9.4 %
Activella™ (Pharmacia, 2000)	1/0.5	69	-10.5 %	-12.4%	-10.8%	+2.2%
Femhrt™ (Speroff, 1996)	1/0.05	132	-7.0 %	-6.7 %	-7.5 %	+12.1 %
PremPro® (PEPI Group, 1995)	0.625/2.5	174	-14.0 mg/dL	+1.2 mg/dL	-16.5 mg/dL	+11.4 mg/dL
Estratest® (Raisz, 1996)	1.25/2.5	13	-11.5 %	-23.0 %	-4.9 %	-32.4 %
Estratest® (Watts, 1995)	1.25/2.5	22	-9.1 mg/dL	-16.4 mg/dL	+1.9 mg/dL	-30.0 mg/dL
Estratest® (Barrett-Connor, 1999)	1.25/2.5	55	-24.2 mg/dL	-17.3 mg/dL	-6.0 mg/dL	-22.6 mg/dL
Estratest HS® (Barrett-Connor, 1999)	.625/1.25	69	-25.0 mg/dL	-14.9 mg/dL	-6.8 mg/dL	-28.7 mg/dL
Estratest HS® (Hickok, 1993)	.625/1.25	13	-33.3 mg/dL	-14.5 mg/dL	-19.3 mg/dL	+3.4 mg/dL

* Generic version used in study

The effect of Cenestin™ on blood lipids has not been evaluated. It is expected to be similar to those observed with Premarin®. The effect of PremPhase® on blood lipids was evaluated in 36 women (Lobo, 1994) and led to an 11.1% reduction in lipoprotein (a) levels. The other lipid parameters were studied, but specific values were not given.

Adverse Reactions:

Adverse Reactions Reported (%) in the Product Package Inserts

	Cenestin™ 0.625-1.25 mg (N=72)	Premarin® 0.625 mg (N=347)	Ortho-Prefest™ (N=579)	Activella™ 1/0.5 (N=295)	Femhrt™ 1/.05 (N=258)	PremPro® 0.625/2.5 (N=340)	PremPhase® 0.625/5.0 (N=351)
Headache	68	38	23	16	18.2	36	37
Nausea/Vomiting	25	11	6	3	7.4	11	11
Abdominal Pain	28	17	12		8.1	16	23
Arthralgia	25	7	9		5.8	9	9
Myalgia	28		5		7.8		
Depression	28	10	5		5.8	6	11
Nervousness	28				5.4		
Breast Pain	29	12	16	24	8.1	33	32
UTI					6.2		
Vaginitis		3	7	4	5.4	7	5
Insomnia	42			6			
Asthenia	33	8				6	10

The adverse events reported with oral estrogens are qualitatively similar and are viewed as such by the FDA. The above table lists the incidence (% of patients) of reported adverse reactions taken from the individual product package inserts. These numbers are thus *not directly comparable* as the study populations, study design and the method of determining adverse event rates differ among the trials. In addition, the rates of the above reported adverse events does not list the placebo arm, in which many of the adverse events (such as headache) were comparable (active drug to placebo). Although there are a limited number of comparative trials available, the incidences of adverse events reported in these trials are generally similar. The package inserts for the remaining products (those not included in the table) list only the adverse reactions of the entire class and do not provide incidence data for the specific product.

A report reviewed the post-marketing safety surveillance of the methyltestosterone containing products, Estratest® and Estratest HS®, from 1989 through 1996 (Phillips, 1997). The most commonly reported adverse effects included weight gain, headache, nausea, vasodilation, acne, alopecia, and hirsutism. Virilizing effects are typically dose and duration dependent and can be managed by dose reduction or discontinuation.

Drug Interactions:

The following drug interactions are noted for the estrogen class as a whole:

Estrogen Drug Interactions			
Precipitant Drug	Object Drug*		Description
Estrogens	Oral anticoagulants	↓	Estrogens may theoretically reduce the hypoprothrombinemic effect of anticoagulants.
Estrogens	Tricyclic antidepressants	↔	Pharmacologic effects of these agents may be altered by estrogens; the effects of this interaction may depend on the dose of the estrogen. An increased incidence of toxic reactions may also occur.
P450 inducers Rifampin Barbiturates	Estrogens	↓	Coadministration of barbiturates, rifampin, and other agents that induce hepatic microsomal enzymes may produce lower estrogen levels than expected.
Estrogens	Corticosteroids	↑	An increase in the pharmacologic and toxicologic effects of corticosteroids may occur via inactivation of hepatic P450 enzyme.
Hydantoins	Estrogens	↓	Breakthrough bleeding, spotting, and pregnancy have resulted when these medications were used concurrently. A loss of seizure control has also been suggested and may be due to fluid retention
Estrogens	Hydantoins		

* ↑ = Object drug increased. ↓ = Object drug decreased. ↔ = Undetermined clinical effect.
Adapted from Facts and Comparisons, pg. 219, 2000.

No specific drug interactions are noted on the product labeling for the estrogen-only products.

The following drug interactions are seen with progestins:

Progestin Drug Interactions			
Precipitant Drug	Object Drug*		Description
Aminoglutethimide	Medroxyprogesterone	↓	Aminoglutethimide may increase the hepatic metabolism of medroxyprogesterone, possibly decreasing its therapeutic effects.
Rifampin	Norethindrone	↓	Rifampin may reduce the plasma levels of norethindrone via hepatic microsomal enzyme induction, possibly decreasing its pharmacologic effects.

* ↑ = Object drug increased. ↓ = Object drug decreased. ↔ = Undetermined clinical effect.
Adapted from Facts and Comparisons, pg. 229, 2000.

Medroxyprogesterone is the progestin component of PremPro® and PremPhase®. Norethindrone is the progestin component of Femhrt™. No specific drug interactions are noted on the product labeling for the estrogen-progestin combination products.

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The following drug interactions are seen with methyltestosterone:

Methyltestosterone Drug Interactions			
Precipitant Drug	Object Drug*		Description
Methyltestosterone	Anticoagulants	↑	The anticoagulant effect may be potentiated by 17-alkyl-testosterone derivatives such as methyltestosterone. Although the non-17-alkylated agent (testosterone) appears safer, at least one case report described a similar interaction. Avoid concomitant use if possible.
Methyltestosterone	Imipramine	↔	Coadministration results in a dramatic paranoid response in four of five patients.

* ↑ = Object drug increased. ↓ = Object drug decreased. ↔ = Undetermined clinical effect.
Adapted from Facts and Comparisons, pg. 260, 2000.

Methyltestosterone is the androgen component of Estratest® and Estratest HS®. Additional drug interactions noted on the Estratest® and Estratest HS® include:

- Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.
- The metabolic effects of androgens may decrease blood glucose and insulin requirements in diabetic patients.

Dosing And Availability

Formulation	Tablet Strength	Dosing	AWP/Day*
Esterified Estrogens (Estratab®, various)	0.3, 0.625, 2.5 mg (1.25 mg available by generic only) * Solvay currently reports disruption of the manufacture of the 0.3 mg strength of Estratab®.	*Treatment of moderate to severe vasomotor symptoms:* 1.25 mg once daily administered cyclically (e.g. three weeks on and one week off). *Treatment of atrophic vaginitis and kraurosis vulvae:* 0.3 to ≥ 1.25 mg daily administered cyclically. *Treatment of female hypogonadism:* Administer 2.5-7.5 mg daily in divided doses for 20 days followed by a 10-day rest period. *Treatment of female castration and primary ovarian failure:* Administer 1.25 mg daily cyclically. Adjust to lowest level providing effective control. *Treatment of inoperable progressive prostate cancer:* 1.25-2.5 mg three times a day. *Treatment of inoperable progressive breast cancer:* 10 mg three times a day in selected men and postmenopausal women. *Osteoporosis prevention:* Initiate at 0.3 mg daily as soon as possible after menopause, increasing to 1.25 mg a day as necessary.	Estratab® 0.3 mg = $ 0.46 0.625 mg = $ 0.62 2.5 mg = $ 1.48
Synthetic Conjugated Estrogens A (Cenestin™)	0.625, 0.9, 1.25 mg	*Treatment of moderate to severe vasomotor symptoms:* The lowest dosage that will control symptoms should be used. The initial recommended dose is 0.625 mg daily with titration up to 1.25 mg daily.	Cenestin® 0.625 mg = $ 0.52 0.9 mg = $ 0.63 1.25 mg = 0.63

Formulation	Tablet Strength	Dosing	AWP/Day
Conjugated Estrogens [Equine] (Premarin®)	0.3, 0.625, 0.9, 1.25, 2.5 mg	*Treatment of moderate to severe vasomotor symptoms:* 1.25 mg daily. Start cyclic administration arbitrarily if patient has not menstruated in ≥ 2 months. *Treatment of atrophic vaginitis and urethritis:* 0.3 to ≥ 1.25 mg daily administered cyclically. *Treatment of female hypogonadism:* Administer 2.5-7.5 mg daily in divided doses for 20 days followed by a 10-day rest period. *Treatment of female castration and primary ovarian failure:* Administer 1.25 mg daily cyclically. Adjust to lowest level providing effective control. *Treatment of prostate cancer (for palliation, advanced androgen dependent):* 1.25-2.5 mg three times a day. *Treatment of breast cancer for palliation in appropriately selective women and men with metastatic disease:* 10 mg three times a day. *Osteoporosis prevention:* 0.625 mg daily administered cyclically.	Premarin® 0.3 mg = $ 0.47 0.625 mg = $ 0.61 0.9 mg = $ 0.78 1.25 mg = $ 0.90 2.5 mg = $ 1.54
Estropipate (Ogen®, various)	0.625, 1.25, 2.5 mg	*Treatment of moderate to severe vasomotor symptoms and vulval and vaginal atrophy:* 0.625-5.0 mg daily; administer lowest effective dose. *Treatment of female hypogonadism, female castration, or primary ovarian failure:* Administer 1.25-7.5 mg daily for three weeks followed by an 8-10 day rest period. *Osteoporosis prevention:* 0.625 mg daily for 25 days of a 31-day cycle per month.	Ogen® 0.625 mg = $ 0.76 1.25 mg = $ 1.05 2.5 mg = $ 1.83

Formulation	Tablet Strength	Dosing	AWP/Day
Ethinyl Estradiol (Estinyl®)	0.02, 0.05 mg (0.5 mg dose has been discontinued)	*Treatment of moderate to severe vasomotor symptoms:* Usual dosage range is 0.02-0.05 mg a day given cyclically. *Treatment of female hypogonadism:* 0.05 mg one to three times a day during the first two weeks of a theoretical menstrual cycle. *Treatment of inoperable, progressive breast cancer:* 1 mg three times a day in appropriately selected postmenopausal women. *Treatment of inoperable, progressive prostate cancer:* 0.15-2.0 mg given chronically.	Estinyl® 0.02 mg = $ 0.37 0.05 mg = $ 0.65
Micronized Estradiol (Estrace®, various)	0.5, 1.0, 2.0 mg	*Treatment of signs and symptoms of menopause, vulval or vaginal atrophy, female hypogonadism, female castration, or primary ovarian failure:* Initial dose: 1-2 mg once daily administered cyclically. Maintenance dose: Reduce dose at 3 month intervals as tolerated. *Prevention of osteoporosis*: Initiate dose at 0.5 mg daily administered cyclically, titrate dose to control concurrent menopausal symptoms. *Treatment of breast cancer with metastatic disease (palliative therapy only)*: 10 mg three times daily for at least three months. *Treatment of advanced androgen-dependent carcinoma of the prostate (palliative therapy only)*: 1-2 mg three times daily.	Estrace® 0.5 mg = $ 0.39 1.0 mg = $ 0.44 2.0 mg = $ 0.50

Formulation	Tablet Strength	Dosing	AWP/Day
Estradiol plus Norgestimate (Ortho-Prefest™)	1.0 mg Estradiol 0.09 mg Norgestimate	*Treatment of moderate to severe vasomotor symptoms and vulval and vaginal atrophy associated with menopause:* Continuous repetition of estradiol 1 mg/d for 3 days followed by estradiol 1 mg/d plus norgestimate 0.09 mg/d. *Prevention of osteoporosis:* Continuous repetition of estradiol 1 mg/d for 3 days followed by estradiol 1 mg/d plus norgestimate 0.09 mg/d.	Ortho-Prefest™ 1.0/0.09 = ???
Estradiol plus Norethindrone Acetate (Activella™)	1.0 mg Estradiol 0.5 mg Norethindrone Acetate	*Treatment of moderate to severe vasomotor symptoms:* One tablet daily for 28 days / cycle. *Prevention of osteoporosis*: One tablet daily for 28 days / cycle.	Activella™ 1.0/0.5 = 0.93
Ethinyl Estradiol plus Norethindrone Acetate (Femhrt™)	0.05 mg Ethinyl Estradiol 1.0 mg Norethindrone Acetate	*Treatment of moderate to severe vasomotor symptoms:* One tablet daily for 28 days / cycle. *Prevention of osteoporosis*: One tablet daily for 28 days / cycle.	Femhrt™ 0.05/1.0 = 0.79
Conjugated Estrogens plus Medroxyprogesterone Acetate (PremPro®)	0.625 mg Conjugated Estrogens 2.5, 5.0 mg Medroxyprogesterone Acetate	*For menopause, vulval/vaginal atrophy, and osteoporosis prevention:* The recommended dose is either (A) one 0.625 mg/2.5 mg tablet daily or (B) one 0.625mg conjugated estrogen tablet once daily on days 1-14 and one 0.625 mg/ 5.0 mg tablet daily on days 15-28.	PremPro® 0.625/2.5 = $ 1.02 0.625/5.0 = $ 1.02
Conjugated Estrogens plus Medroxyprogesterone Acetate (PremPhase®)	0.625 mg Conjugated Estrogens 5.0 mg Medroxyprogesterone Acetate		PremPhase® 0.625/5.0 = $ 0.94

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Formulation	Tablet Strength	Dosing	AWP/Day
Esterified Estrogens plus Methyltestosterone (Estratest®)	1.25 mg Esterified Estrogens 2.5 mg Methyltestosterone	*Treatment of moderate to severe symptoms:* One Estratest® or one to two **Estratest HS® tablets** daily administered cyclically (e.g. **three weeks on and one** week off).	Estratest® 1.25/2.5 = $ 1.21
Esterified Estrogens plus Methyltestosterone (Estratest HS®)	0.625 mg Esterified Estrogens 1.25 mg Methyltestosterone		Estratest HS® 0.625/1.25 = $ 0.93

* AWP from Drug Topics Red Book Online, November 1, 2000. AWP is for branded products only (generic prices will vary).

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Conclusion:

All of the products examined in this class review are efficacious for the treatment of their labeled indications. The shortage of comparative trials examining two or more products makes direct clinical comparisons difficult. Nearly all of the comparative trials of the estrogen-only products compare Premarin® to another product, and the results show similar efficacy and safety between the products. We have been unable to locate any comparative trials between the estrogen-progestin combination products. The efficacy and side effect profiles appear similar between the available agents. The estrogen-androgen products are effective for those women not responding to estrogen alone; studies have also documented their effectiveness for several unlabeled uses.

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